REMARKS

In the Office Action dated March 11, 2003, claims 1-16 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection was based on the use of the term "pre-existing expert rules" which was introduced in the last Amendment. The use of this term was merely for the purpose of indicating that the expert system starts operation with an initial or original set of expert rules. This was merely intended to provide a designation or name for those rules, in order to better differentiate them from the "new" rules that are created using all of the point of care raw data and all of the clinical data. The term "new expert rule" has been replaced in the present Amendment by "modified expert rule," which is supported in the specification as originally filed at least in the paragraph beginning at page 4, line 4. Each of independent claims 1 and 9 has been amended in this manner.

A typographical error in claim 1 also has been corrected (changing "composed" to "compared").

Since it is beyond question that the expert system described in the present specification, as any expert system, must begin with a certain initial set of expert rules, this was all that was intended to be meant by the term "pre-existing expert rules." Since this term has now been cancelled from the claims (resulting, in the opinion of the Applicants, the independent claims now being less clear), and since the term "new expert rules" has been replaced by the term "modified expert rules" which finds explicit support in the specification as originally filed, no new matter is

present in any of claims 1-16 and the aforementioned rejection is respectfully submitted to be overcome.

Claims 1-16 also were rejected under §112, first paragraph, on the basis of an alleged lack of enablement. Claims 1-16 also were rejected as being vague and indefinite under §112, second paragraph. Applicants will address the rejection under §112, second paragraph first, since this has a bearing on the lack of enablement rejection.

Claims 1 and 9 were rejected under §112, second paragraph as being vague and indefinite because of the use of the term "improved diagnostic utility." This term has now been replaced with the term "improved diagnostic specificity." This is supported in the specification as originally filed at page 8, line 12. Whether a diagnostic result has improved specificity compared to another diagnostic result can be easily empirically determined without undue experimentation. There are of course many ways by which "specificity" can be measured, and any one of such criteria can be used. It is not the intention of the Applicants to provide any limitations (nor are any such limitations needed) in order to inform a person of ordinary skill in the art when, and under what conditions, a diagnostic result is more specific than another. Those of ordinary skill in the art are readily capable of identifying one or more criteria for this purpose.

This feature of claims 1 and 9 also is relevant to the "lack of enablement" rejection. The Examiner is artificially imposing a much higher level of dedicated or directed utility for the subject matter disclosed and claimed in the present application than was ever intended by the Applicants. More importantly, such a high level of

dedicated utility is not necessary to allow those of ordinary skill in the relevant art to make and use the invention.

The details, or the specific purpose, of the evaluation system that includes an expert system are not important to the use and operation of the subject matter of claims 1 and 9. It is only necessary that information be gathered from a plurality of disposable biochips from a plurality of patients, and that this information include multiple biomolecular markers, and that point of care information be obtained from at least one of the biochips and that clinical data be obtained which is composed of a diagnostic result and the additional information set forth in the claims, and that the rules employed by the evaluation system be modified using all of the point of care raw data and all of the clinical data. As noted above, the goal of producing the modified expert rule is for the expert rule to have improved diagnostic specificity compared to initial expert rules.

The exact nature of the expert rules, and the goal or intended result that they are to achieve, are not important to the subject matter of the invention. It is only important that at least one of the original rules be modified so as to improve the diagnostic specificity. This is an easily ascertainable standard.

The Examiner already has made of record a number of expert systems, which are known in the art, some of which are suitable for use in the evaluation of medical data. A further example of such a known system is described in PCT Application WO 97/29447, a copy of which is attached hereto. Any of those expert systems disclosed in the references can be made more specific by the present invention, but none of those references discloses or suggests the compilation of the data, or the

use of the data, which are set forth in independent claims 1 and 9 in order to generate a modified new rule having diagnostic specificity.

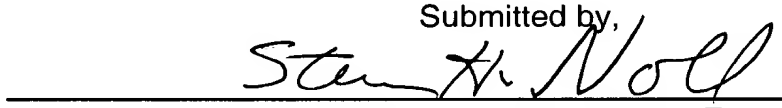
The Examiner also questioned whether the details of the biochip of the type used in the present invention have been adequately disclosed. An example of a publication describing a biochip suitable for use in the present invention is also attached hereto (NanoChip™ Electronic Microarray). The Examiner cited a statement in the present disclosure that biochips are "about to enter widespread use" as calling into question whether such biochips would have been readily available to practice the claimed invention. The Examiner's conclusion does not logically follow from the statement in the disclosure. Stating that an item is not in widespread use does not mean that the item is not known or accessible, it simply means that it has not yet reached a state of universal usage. §112, first paragraph, however, merely requires that an item be known to those of ordinary skill in the art, and whether such an item is in "widespread use" is irrelevant to that criterion. As long as it is known, that is all that is necessary to satisfy §112, first paragraph.

The aforementioned publications are provided hereto solely as evidence-substantiating knowledge that the Applicants have already admitted is well known to those of ordinary skill in the art. These documents were provided by the Applicants' German representative, and the undersigned counsel does not know whether they have been known to the Applicants more than three months prior to the filing of this response. If they had been known for more than three months, submitting those references in an Information Disclosure Statement would require payment of an additional fee. Since these documents merely demonstrate knowledge that the Applicants have already admitted is known in the art, paying the additional fee to

make this admitted prior art officially of record is not seen to be necessary. The Examiner, of course, is free to cite these references and therefore make them "officially" of record if the Examiner believes this would be beneficial.

In summary, Applicants respectfully submit that the prior art of record in the present application amply demonstrates that those of ordinary skill in the art are well aware of the use and operation of expert systems. The present disclosure provides sufficiently detailed instructions, within the context of that known information, to enable those of ordinary skill in the art to make and use the invention. All claims of the application are therefore submitted to be in full compliance with all provisions of §112, first and second paragraphs. Early reconsideration of the application is respectfully requested.

Submitted by,



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(54) Title: METHOD FOR SELECTING MEDICAL AND BIOCHEMICAL DIAGNOSTIC TESTS USING NEURAL NETWORK-RELATED APPLICATIONS

(57) Abstract

Methods are provided for developing medical diagnostic tests using decision-support systems, such as neural networks. Patient data or information, typically patient history or clinical data, are analyzed by the decision-support systems to identify important or relevant variables and decision-support systems are trained on the patient data. Patient data are augmented by biochemical test data, or results, where available, to refine performance. The resulting decision-support systems are employed to evaluate specific observation values and test results, to guide the development of biochemical or other diagnostic tests, to assess a course of treatment, to identify new diagnostic tests and disease markers, to identify useful therapies, and to provide the decision-support functionality for the test. Methods for identification of important input variables for medical diagnostic tests for use in training the decision-support systems to guide the development of the tests, for improving the sensitivity and specificity of such tests, and for selecting diagnostic tests that improve overall diagnosis of, or potential for, a disease state and that permit the effectiveness of a selected therapeutic protocol to be assessed are provided. The methods for identification can be applied in any field in which statistics are used to determine outcomes. A method for evaluating the effectiveness of any given diagnostic test is also provided.

METHOD FOR SELECTING MEDICAL AND BIOCHEMICAL DIAGNOSTIC TESTS USING NEURAL NETWORK-RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Serial 08/599,275, entitled "METHOD FOR DEVELOPING MEDICAL AND BIOCHEMICAL DIAGNOSTIC TESTS USING NEURAL NETWORKS" to Jerome Lapointe and Duane DeSieno, filed February 9, 1996, and claims priority under 35 U.S.C. §119(e) to U.S. provisional application Serial No. 60/011,449, entitled "METHOD AND APPARATUS FOR AIDING IN THE DIAGNOSIS OF ENDOMETRIOSIS USING A PLURALITY OF PARAMETERS SUITED FOR ANALYSIS THROUGH A NEURAL NETWORK" to Jerome Lapointe and Duane DeSieno, filed February 9, 1996.

The subject matter of each of the above-noted application and provisional application is herein incorporated in its entirety by reference thereto.

MICROFICHE APPENDIX

Two computer Appendices containing computer program source code for programs described herein have been submitted concurrently with the filing of this application. The Computer Appendices will be converted to a Microfiche Appendices pursuant to 37 C.F.R. 1.96(b). The Computer Appendices, which are referred to hereafter as the "Microfiche Appendices, are each incorporated herein by reference in its entirety.

Thus, a portion of the disclosure of this patent document contains material that is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or patent disclosure, as it appears in the Patent and Trademark Office patent file or records, but otherwise reserves all copyright rights whatsoever.

the output of the processing element is determined by a typically non-linear transfer function. In a typical model for neural networks, the processing elements are arranged into an input layer for elements which receive inputs, an output layer containing one or more elements which generate an output, and one or more hidden layers of elements therebetween. The hidden layers provide the means by which non-linear problems may be solved. Within a processing element, the input signals to the element are weighted arithmetically according to a weight coefficient associated with each input. The resulting weighted sum is transformed by a selected non-linear transfer function, such as a sigmoid function, to produce an output, whose values range from 0 to 1, for each processing element. The learning process, called "training", is a trial-and-error process involving a series of iterative adjustments to the processing element weights so that a particular processing element provides an output which, when combined with the outputs of other processing elements, generates a result which minimizes the resulting error between the outputs of the neural network and the desired outputs as represented in the training data. Adjustment of the element weights are triggered by error signals. Training data are described as a number of training examples in which each example contains a set of input values to be presented to the neural network and an associated set of desired output values.

A common training method is backpropagation or "backprop", in which error signals are propagated backwards through the network. The error signal is used to determine how much any given element's weight is to be changed and the error gradient, with the goal being to converge to a global minimum of the mean squared error. The path toward convergence, i.e., the gradient descent, is taken in steps, each step being an adjustment of the input weights of the processing element. The size

When neural networks are trained on sufficient training data, the neural network acts as an associative memory that is able to generalize to a correct solution for sets of new input data that were not part of the training data. Neural networks have been shown to be able to operate even in the absence of complete data or in the presence of noise. It has also been observed that the performance of the network on new or test data tends to be lower than the performance on training data. The difference in the performance on test data indicates the extent to which the network was able to generalize from the training data. A neural network, however, can be retrained and thus learn from the new data, improving the overall performance of the network.

Neural nets, thus, have characteristics that make them well suited for a large number of different problems, including areas involving prediction, such as medical diagnosis.

Neural Nets and Diagnosis

In diagnosing and/or treating a patient, a physician will use patient condition, symptoms, and the results of applicable medical diagnostic tests to identify the disease state or condition of the patient. The physician must carefully determine the relevance of the symptoms and test results to the particular diagnosis and use judgement based on experience and intuition in making a particular diagnosis. Medical diagnosis involves integration of information from several sources including a medical history, a physical exam and biochemical tests. Based upon the results of the exam and tests and answers to the questions, the physician, using his or her training, experience and knowledge and expertise, formulates a diagnosis. A final diagnosis may require subsequent surgical procedures to verify or to formulate. Thus, the process of diagnosis involves a combination of decision-support,

issues relating to the development of practical diagnostic tests for a wide range of conditions and does not address the selection of input variables.

Computerized decision-support methods other than neural networks have been reported for their applications in medical diagnostics, including knowledge-based expert systems, including MYCIN (Davis, et al., "Production Systems as a Representation for a Knowledge-based Consultation Program", Artificial Intelligence, 1977; 8: 1: 15-45) and its progeny TEIRESIAS, EMYCIN, PUFF, CENTAUR, VM, GUIDON, SACON, ONCOCIN and ROGET. MYCIN is an interactive program that diagnoses certain infectious diseases and prescribes anti-microbial therapy. Such knowledge-based systems contain factual knowledge and rules or other methods for using that knowledge, with all of the information and rules being pre-programmed into the system's memory rather than the system developing its own procedure for reaching the desired result based upon input data, as in neural networks. Another computerized diagnosis method is the Bayesian network, also known as a belief or causal probabilistic network, which classifies patterns based on probability density functions from training patterns and *a priori* information. Bayesian decision systems are reported for uses in interpretation of mammograms for diagnosing breast cancer (Roberts, et al., "MammoNet: A Bayesian Network diagnosing Breast Cancer", Midwest Artificial Intelligence and Cognitive Science Society Conference, Carbondale, IL, April 1995) and hypertension (Blinowska, et al. (1993) "Diagnostica -- A Bayesian Decision-Aid System -- Applied to Hypertension Diagnosis", IEEE Transactions on Biomedical Engineering 40:230-35) Bayesian decision systems are somewhat limited in their reliance on linear relationships and in the number of input data points that can be handled, and may not be as well suited for decision-support involving non-linear relationships between variables. Implementation of Bayesian methods using the

present in a significant proportion of these women. Thus, endometriosis represents an example of a disease state in which a physician must draw upon experience using a complex set of information to formulate a diagnosis. The validity of the diagnosis is related to the experience and ability of the physician.

As a result, determining if a woman has endometriosis from symptoms alone has not been possible. Within the medical community, the diagnosis of endometriosis is confirmed only by direct visualization of endometrial lesions during surgery. Many physicians often impose a further restriction and demand that the suspected lesions be verified as being endometrial-like (glands and stroma) using histology on endometrial biopsied tissue. Thus, a non-invasive diagnostic test for endometriosis would be of significant benefit.

Therefore, it is an object herein to provide a non-invasive diagnostic aid for endometriosis. It is also an object herein to provide methods to select important variables to be used in decision-support systems to aid in diagnosis of endometriosis and other disorders and conditions. It is also an object herein to identify new variables, identify new biochemical tests and markers for diseases and to design to new diagnostic tests that improve upon existing diagnostic methodologies.

SUMMARY OF THE INVENTION

Methods using decision-support systems for the diagnosis of and for aiding in the diagnosis of diseases, disorders and other medical conditions are provided. The methods provided herein, include a method of using patient history data and identification of important variables to develop a diagnostic test; a method for identification of important selected variables; a method of designing a diagnostic test; a method of evaluating the usefulness of diagnostic test; a method of expanding clinical utility of diagnostic test, and a method of selecting a course of

are identified through the use of a decision-support system or systems, such as a neural network or a consensus of neural networks; and another set of decision-support systems is trained on the identified subset(s) to produce a consensus decision-support system based test, such as a neural net-based test for the condition. The use of consensus systems, such as consensus neural networks, minimizes the negative effects of local minima in decision-support systems, such as neural network-based systems, thereby improving the accuracy of the system.

Also, to refine or improve performance, the patient data can be augmented by increasing the number of patients used. Also biochemical test data and other data may be included as part of additional examples or by using the data as dditional variables prior to the variable selection process.

The resulting systems are used as an aid in diagnosis. In addition, as the systems are used patient data can be stored and then used to further train the systems and to develop systems that are adapted for a particular genetic population. This inputting of additional data into the system may be implemented automatically or done manually. By doing so the systems continually learn and adapt to the particular environment in which they are used. The resulting systems have numerous uses in addition to diagnosis, which includes assessing the severity of a disease or disorder, predicting the outcome of a selected treatment protocol. The systems may also be used to assess the value of other data in a diagnostic procedure, such as biochemical test data and other such data, and to identify new tests that are useful for diagnosing a particular disease.

without biochemical data may be sufficient to obviate the need for invasive surgical diagnostic procedures.

Also provided herein is a method of identifying and expanding clinical utility of diagnostic test. The results of a particular test, particular one that had heretofore not been considered of clinical utility with respect to the disorder or condition of interest, are combined with the variables and used with the decision-support system, such as a neural net. If the performance, the ability to correctly diagnose a disorder, of the system is improved by addition of the results of the test, then the test will have clinical utility or a new utility.

Similarly, the resulting systems can be used to identify new utilities for drugs or therapies and also to identify uses for particular drugs and therapies. For example, the systems can be used to select subpopulations of patients for whom a particular drug or therapy is effective. Thus, methods for expanding the indication for a drug or therapy and identifying new drugs and therapies are provided.

In specific embodiments, neural networks are employed to evaluate specific observation values and test results, to guide the development of biochemical or other diagnostic tests, and to provide the decision-support functionality for the test.

A method for identification of important variables (parameters) or sets thereof for use in the decision-support systems is also provided. This method, while exemplified herein with reference to medical diagnosis, has broad applicability in any field, such as financial analysis, in which important parameters or variables are selected from among a plurality.

In particular, a method for selecting effective combinations of variables is provided. The method involves: (1) providing a set of "n" candidate variables and a set of "selected important variables", which

data set, where each total for the selected variable represents the relative contribution of each variable to the determination of the decision-support system output. This total will be used to rank each variable according to its relative contribution to the determination of the decision-support system output.

As shown herein, computer-based decision-support systems such as neural networks reveal that certain input factors, which were not initially considered to be important, can influence an outcome. This ability of a neural network to reveal the relevant input factors permits its use in guiding the design of diagnostic tests. Thus a method of designing a diagnostic test, and a method of evaluating utility of diagnostic test are also provided. In each instance, the data from the test or possible test is added to the input of the decision-support system. If the results are improved when the data are included in the input, then the diagnostic test may have clinical utility. In this manner, tests that heretofore were not known to be of value in diagnosis of a particular disorder are identified, or new tests can be developed. Neural networks can add robustness to diagnostic tests by discounting the effects of spurious data points and by identifying other data points that might be substituted, if any.

Networks are trained on one set of variables and then clinical data from diagnostic or biochemical test data and/or additional patient information are added to the input data. Any variable that improves the results compared to their absence is (are) selected. As a result, particular tests that heretofore were of unknown value in diagnosing a particular disorder can be shown to have relevance. For example, the presence or absence of particular spots on a western blot of serum antibodies can be

following combinations of three variables can be used with a decision-support system for diagnosis of endometriosis:

a) number of births, history of endometriosis, history of pelvic surgery;

b) diabetes, pregnancy hypertension, smoking;

c) pregnancy hypertension, abnormal pap smear/dysplasia, history of endometriosis;

d) age, smoking, history of endometriosis;

e) smoking, history of endometriosis, dysmenorrhea;

f) age, diabetes, history of endometriosis;

g) pregnancy hypertension, number of births, history of endometriosis;

h) Smoking, number of births, history of endometriosis;

i) pregnancy hypertension, history endometriosis, history of pelvic surgery;

j) number of pregnancies, history of endometriosis, history of pelvic surgery;

k) number of births, abnormal PAP smear/dysplasia, history of endometriosis;

l) number of births, abnormal PAP smear/dysplasia, dysmenorrhea;

m) history of endometriosis, history of pelvic surgery, dysmenorrhea; and

n) number of pregnancies, history of endometriosis, dysmenorrhea.

Diagnostic software and exemplary neural networks that use the variables for diagnosis of endometriosis are also provided. The software generates a clinically useful endometriosis index.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a flow chart for developing a patient-history-based diagnostic test process.

FIGURE 2 is a flow chart for developing a biochemical diagnostic test.

FIGURE 3 is a flow chart of the process for isolating important variables.

FIGURE 4 is a flow chart on the process of training one or a set of neural networks involving a partitioning of variables.

FIGURE 5 is a flow chart for developing a biochemical diagnostic test.

FIGURE 6 is a flow chart for determining the effectiveness of a biochemical diagnostic test.

FIGURE 7 is a schematic diagram of a neural network trained on clinical data of the form used for the consensus network of a plurality of neural networks.

FIGURE 8 is a schematic diagram of a second embodiment of a neural network trained on clinical data augmented by test results data of the form used for the consensus of eight neural networks.

FIGURE 9 is a schematic diagram of a processing element at each node of the neural network.

FIGURE 10 is a schematic diagram of a consensus network of eight neural networks using either the first or second embodiment of the neural network.

FIGURE 11 is a depiction of an exemplary interface screen of the user interface in the diagnostic endometriosis index.

The NanoChip® Electronic Microarray is housed in the NanoChip® Cartridge.

NanoChip® Electronic Microarray

Chip Size
0.7 cm square

Array Dimensions
2 mm square

Test Site Size
80 microns

Distance between Site Centers
200 microns

Number of Test Sites
100

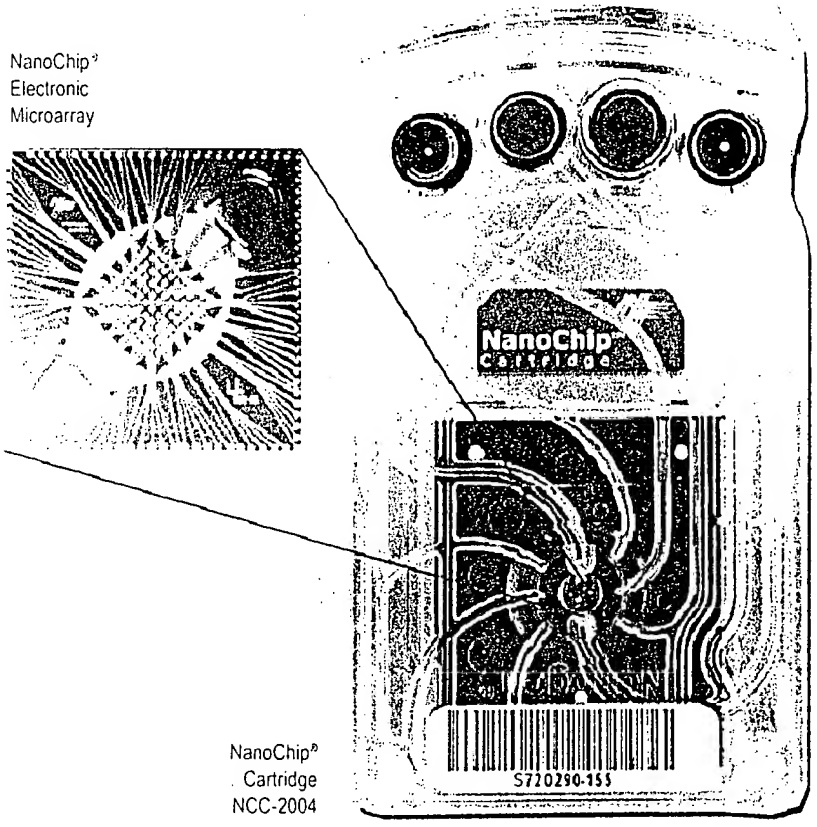
Permeation Layer
Thin hydrogel layer incorporating streptavidin

Binding Chemistry on the Test Sites
Electronically-driven streptavidin/biotin binding

Maximum Loading Density
Approximately 10^9 fragments per site

Minimum Sample Volume
60 µL

Storage Conditions
2–8°C



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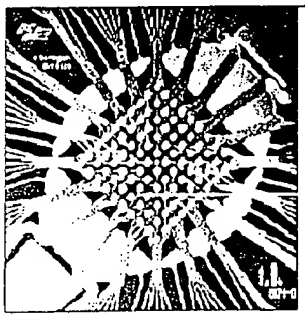
CERTAINTY | CONTROL | CONSOLIDATION

NanoChip® Electronic Microarray



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ELECTRICITY The NanoChip® Electronic Microarray has 100 test sites and extends its power through the use of electricity. Nucleic acids, DNA and RNA, are charged and can be moved or concentrated electronically. By positively or negatively charging test sites, the NanoChip® array can control assay conditions providing a number of advantages.

The NanoChip® array uses **ELECTRICITY** in a **REVOLUTIONARY** way to improve molecular testing. The automated Molecular Biology Workstation makes molecular testing **ROUTINE.** NANOGEN IS MAKING THE REVOLUTIONARY ROUTINE™.

In the research setting, we have found:

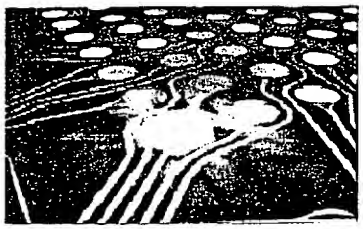
CERTAINTY To date, the NanoChip® System has been proven to approach 100% accuracy and has corrected both DNA sequence data and the results from RT-PCR and RFLP.

CONTROL Unique to the NanoChip® array, reactions only occur at charged test sites. The user can therefore use one, ten, fifty or any number of test sites as required. Remaining test sites can be saved for future use.

CUSTOMIZABLE The open nature of the NanoChip® array allows customers to design and run their own assays in their lab. Nanogen also provides a predefined menu of more commonly used assays.

MULTIPLEXING A key advantage of microarray technology is its ability to do multiple analyses on a single sample. Molecular testing is predicted to move rapidly in this direction.

SPEED Driving the reactions electronically significantly increases assay speed and throughput.



Electronically charging a test site on the NanoChip® Electronic Microarray.

Nanogen®

For laboratory use only.